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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/24/2003

Richard Daifuku

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EXAMINER

OLSON, ERIC

ART UNIT

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1623

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/670,915	Applicant(s) DAIFUKU ET AL.	
	Examiner Eric S. Olson	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 8-15 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 8-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Detailed Action

This office action is a response to applicant's communication submitted October 30, 2007 wherein rejections of record in the previous office action are traversed. This application claims benefit of provisional application 60/413337, filed September 24, 2002.

Claims 1 and 8-15 are pending in this application.

Claims 1 and 8-15 as amended are examined on the merits herein.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 30, 2007 has been entered.

The declaration of Dimitri Sergueev and accompanying arguments, submitted October 30, 2007, has been fully considered as applied to the grounds of rejection of record in the previous office action. The declaration is found to be persuasive to remove the rejection of instant claims 1 and 8-15 under 35 USC 103(a) for being obvious over Driscoll et al. in view of Wierenga in view of Meyer, as none of the cited references provide motivation for making a nonaromatic compound. Therefore the rejection is withdrawn.

The following new grounds of rejection are introduced:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims are drawn to a compound having a linker that is cleaved *in vivo* after entry into a cell. Covalent linkers are cleaved by various hydrolytic or other enzymes found inside the living cell. Because these enzymes differ between various different cells, the scope of the claim depends on what cell the compound is administered to. The claims and the specification fail to provide any limiting definition of what cell is being considered in the limits of this claim, either in terms of what species the cell is from or what tissue in a multicellular organism. Therefore the limitations of the claim are seen to be indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Powell et al. (Reference included with PTO-892) Powell et al. discloses the compound dihydro-5-aza-cytidine, which is a compound of the claimed invention wherein $R^3 = H$, $R^4 = R^5 = OH$, $R^6 = OH$, $R^8 = R^9 = R^{10} = H$, which is disclosed to be a hydrolytically stable analog of 5-azacytidine with antileukemic activity. (p. 117, left column, first paragraph of the introduction, right column first paragraph) Powell et al. does not disclose a compound wherein R^8 is an alkyl group such as methyl.

It would have been obvious to one of ordinary skill in the art at the time of the invention to make the $R^8 = \text{methyl}$ derivative of the dihydro-5-aza-cytidine compound of Powell et al. One of ordinary skill in the art would have expected the methylated derivative to possess the same activity as the parent compound. It is well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results. See *In re Lincoln*, 126 USPQ 477, 53 USPQ 40 (CCPA 1942); *In re Druey*, 319 F.2d 237, 138 USPQ 39 (CCPA 1963); *In re Lohr*, 317 F.2d 388, 137 USPQ 548 (CCPA); *In re Hoehsema*, 399 F.2d 269, 158 USPQ 598 (CCPA 1968); *In re Wood*, USPQ 148 (CCPA 1977); *Ex parte Fauque*, 121 USPQ 425 (POBA 1954); *Ex parte Henkel*, 130 USPQ 474, (POBA 1960)

Thus the invention taken as a whole is *prima facie* obvious.

Claims 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Powell et al. (Reference included with PTO-892) as applied to claim 1 above, and further in view of Cullis et al. (US patent 6852334, cited in PTO-892) the disclosure of

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Powell et al. is discussed above. Powell et al. does not disclose a composition further comprising an amphiphilic species and a dendrimeric polyamine according to instant claims 12-15.

Cullis et al. discloses conjugates that can be incorporated into stabilized plasma lipid particles comprising a lipid anchor, a non-immunogenic polypeptide, and a polycationic moiety, and further comprising a bioactive agent and a second lipid. (column 2 line 33 – column 3 line 23) The polycationic moiety can have between 2-15 positive charges, derived from basic amino acids or amines, for example tetralysine, as well as polycationic dendrimers. (column 13 lines 17-32) These polycations thus include compounds reasonably considered to be polyamines, and one of ordinary skill in the art would recognize polyamine dendrimers as being another useful embodiment of this species. These conjugates are incorporated into lipid-based drug formulations such as liposomes, composed of specific lipids such as phospholipids which are considered to be composed of a hydrophobic domain and a hydrophilic domain covalently bound to one another. (column 16, lines 11-34) These liposome formulations are useful for delivering bioactive agents such as antineoplastic agents and nucleoside analogs. (column 21 lines 29-60) The formulations are preferably delivered as an aqueous intravenous solution. (column 24 lines 52-60)

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the dihydro-azacytidine compounds of Powell et al. in a formulation containing the liposomes and conjugates of Cullis et al. One of ordinary skill in the art would have been motivated to deliver the drugs in this manner because Cullis

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et al. discloses a method for delivering antineoplastic nucleoside analogs, which would be recognized by one of ordinary skill in the art as including the dihydro-5-azacytidine analogs of Powell et al. One of ordinary skill in the art would reasonably have expected success because formulating a specific known drug in a specific known drug delivery formulation is well within the ordinary and routine level of skill in the art.

Therefore the invention taken as a whole is *prima facie* obvious.

Claims 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Powell et al. (Reference included with PTO-892) as applied to claim 1 above, and further in view of McGuigan et al. (Reference U included with PTO-892) the disclosure of Powell et al. is discussed above. Powell et al. does not disclose a compound wherein R⁶ is as recited in claims 10 and 11.

McGuigan et al. discloses bis(2,2,2-trichloroethyl) phosphate derivatives of AZT showing enhanced membrane penetration and being able to be hydrolyzed to the active phosphate *in vivo*. (p. 355, right column, first paragraph, p. 356 figure 1) These compounds exert an anti-HIV effect by being cleaved intracellularly and trapped inside of the target cell. (p. 357, right column, last paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the compounds of Powell et al. with a bis(2,2,2-trichloroethyl) phosphate group as disclosed by McGuigan et al. One of ordinary skill in the art would have been motivated to make this substitution because McGuigan et al. discloses that the bis(2,2,2-trichloroethyl) phosphate group is a prodrug that releases nucleosides

intracellularly. One of ordinary skill in the art would reasonably have expected success because McGuigan et al. already discloses that this approach works when applied to AZT, a nucleoside analog of similar structure.

Therefore the invention taken as a whole is *prima facie* obvious.

Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Powell et al. (Reference included with PTO-892) as applied to claim 1 above, and further in view of McGuigan et al. 2 (Reference V included with PTO-892) the disclosure of Powell et al. is discussed above. Powell et al. does not disclose a compound wherein R⁶ is as recited in claims 10 and 11.

McGuigan et al. 2 discloses an aryl (2,2,2-trichloroethyl) phosphate derivative of AZT showing enhanced membrane penetration and being able to be hydrolyzed to the active phosphate *in vivo*. (p. 312, first and second paragraphs and figure 1, p. 313 first paragraph) These compounds exert an anti-HIV effect by being cleaved intracellularly and trapped inside of the target cell. (p. 317, last paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the compounds of Powell et al. with an aryl (2,2,2-trichloroethyl) phosphate group as disclosed by McGuigan et al. 2. One of ordinary skill in the art would have been motivated to make this substitution because McGuigan et al. 2 discloses that the an aryl (2,2,2-trichloroethyl) phosphate group is a prodrug that releases nucleosides intracellularly. One of ordinary skill in the art would reasonably

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have expected success because McGuigan et al. 2 already discloses that this approach works when applied to AZT, a nucleoside analog of similar structure.

Therefore the invention taken as a whole is *prima facie* obvious.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/
Examiner, Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623
2/27/2008